REMARKS

Claims 46, 54-77, and 80-107 are pending in the present application. According to the Advisory Action mailed September 4, 2003, the amendment filed on August 12, 2003, was not entered. Independent claims 46 and 76 have been newly amended above to recite "wherein the medicament is in particle form." Support for these amendments may be found throughout the specification as filed, e.g., at page 5, line 5 to line 19.

In part, the invention relates to formulations containing a hydrofluoroalkanes (HFA) propellant, a medicament for inhalation, and an alkyl saccharide surfactant. In the Advisory Action, the Examiner sustained the rejection of claims 46, 54-77, and 80-107 as obvious over WO 91/11495 in view of Neale et al., Sequeira et al., and Meezan et al. Applicants respectfully traverse. As described in detail in the Applicants' response filed August 15, 2003, WO 91/11495, Neale et al., or Sequeira et al., disclose nothing more than the use of non-aqueous organic hydrofluorocarbon propellants with certain surfactants (but not alkyl saccharides). On the other hand, Meezan et al. discloses aqueous formulations: medicaments and alkyl saccharide surfactants dissolved in an aqueous medium (the formulations utilized in Meezan's examples are formulated in saline).

It is beyond question that aqueous formulations and organic hydrocarbon formulations have different chemical and physical properties. As one example, solubility in water and in an HFA can be completely different, and addition of other agents may have opposite effects on solubility in HFA and in water (see Williams et al. (Appendix B), p. 137, esp. Table 4). Even HFAs and CFCs differ; as discussed in McDonald et al. (Appendix A) at page 97, even if a given surfactant has been proven to be useful with the non-aqueous medium CFC, one can't assume it will also be useful with the non-aqueous medium HFA, as their physical and chemical properties are different. HFAs are more polar than CFCs and have different solvency properties (see Appendix A, p. 97). However, CFCs and HFAs are far more similar to each other than HFAs are to water. Thus, one of skill in the art would be aware that a surfactant that behaves in one manner in a given medium may behave very differently in a medium with different properties. Although one of skill in the art might appreciate that the alkyl saccharide surfactant in an aqueous medium was "non-toxic and increase[d] bioavailability of intranasally and buccally

administered medicament" as the Examiner asserts, these properties would by no means be expected to transfer from the aqueous environment that Meezan describes to an organic HFA media. Dispersion forces, polar forces, and hydrogen bonding forces at play in an aqueous solution, especially saline, are known to differ from those in HFAs, and the solubility and subsequent chemical behaviour of a surfactant will depend on those forces. In addition, given the wide range of surfactants known in the art at the time, one of skill in the art, when choosing a surfactant for use in an organic HFA medium, would not have been motivated to select a surfactant previously known only for use with an aqueous medium. Thus, the claimed formulations and methods are not obvious over WO 91/11495 in view of Neale et al., Sequeira et al., and Meezan et al.

In the Advisory Action issued September 4, 2003, the Examiner indicated that the amendment submitted on 15 August 2003 "constitutes new matter" and thus would not be entered. The Applicants had cited at least page 5, lines 5 through 19, in support of the amendment submitted on 15 August, 2003. In a telephone conversation between the Examiner and the undersigned on September 11, 2003, the Examiner indicated that the lack of support rejection centered on the use of the word "solid" in the amendment. It is clear from the specification that the "particles" of medicament comprise solid particles. For example, the specification at page 5, lines 5 through 19, describes medicament particles of a certain diameter. The specification recites, at page 5, lines 14-19:

> Therefore, the medicament for use in the present invention may have to be processed prior to inclusion in the formulations, in order to produce particles in the desired size range. For example the medicament may be micronised, for example out in a suitable mill, for example a jet mill. Alternatively, particles in the desired range may be obtained by for example spray drying or controlled crystallization methods, for example crystallization using supercritical fluids.

It is clear from this passage that the particles are solid particles. Only solid particles could be micronized. Spray drying and controlled crystallization methods both produce solid particles. Further, at page 5, lines 24-25, the specification recites as follows: "When the surfactant and medicament are both micronised, they may be dry mixed and then micronised together, or they may be micronised separately and then mixed." This is a formulation of solid particles; if the

medicament were other than solid particles, this passage would be rendered meaningless. Further support may be found at, e.g., page 5, lines 28-31.

Even though the Applicants believe the claims to be allowable as previously written, and believe the specification to include ample support for "solid particles," the Applicants have amended independent claims 46 and 76 to facilitate prosecution of this application. The claims as amended are drawn to pharmaceutical aerosol formulations comprising a hydrofluoroalkane (HFA) propellant; a physiologically effective amount of a medicament for inhalation; and an alkyl saccharide surfactant, wherein the medicament is in particle form. The teachings of Meezan et al., which, as discussed above and in the previous reply, relate to aqueous formulations of dissolved medicaments, have no relevance for the claimed invention. There would have been no motivation in the art to look to Meezan et al. to find a surfactant that would be useful in a non-aqueous formulation containing particles of medicament, as presently claimed. Nor would there have been any expectation that a surfactant disclosed for use in an aqueous formulation of dissolved medicament could be successfully used in a non-aqueous formulation containing particles of medicament. Thus, the cited art cannot render the present claims obvious.

Finally, claims 46, 54-58, 61-77, 80, 82, 83, and 96-101 remained provisionally rejected for obviousness-type double patenting over claims 1, 10-41, 48-62, 74-105, and 114-127 of U.S. Pat. No. 6,524,557. As noted in the prior action, Applicants will file an appropriate terminal disclaimer once the claims are otherwise deemed allowable.

Please any charges or credits to deposit account 06-1050, referencing attorney docket number 06275-034001.

Respectfully submitted,

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EXHIBIT A

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Transition to CFC-free metered dose inhalers — into the new millennium

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Abstract

Metered dose inhalers (MDIs) are the most popular vehicle for drug delivery into the lungs and some 500 million are manufactured each year. All MDIs marketed prior to 1995 contained chlorofluorocarbons (CFC) as a propellant. These are implicated in the depletion of stratospheric ozone and, except for specific exemptions, their production has been banned since 1996 under the terms of the Montreal Protocol. Hydrofluoroalkanes have been identified as suitable alternatives for MDI propellants but their physico-chemical properties differ significantly from CFCs and an extensive redevelopment and testing programme has been required to demonstrate the safety, quality and efficacy of HFA containing MDIs. Hydrofluoroalkanes contribute to global warming but the benefit to human health through continued MDI availability currently outweighs the environmental concern. Several HFA-MDIs have reached the market and the transition to replace existing CFC-MDIs is now underway. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Metered dose inhalers; Chlorofluorocarbons; Hydrofluoroalkanes

1. Introduction

Delivery of drugs directly to the lower respiratory tract by aerosol inhalation in the treatment of asthma and other respiratory diseases, is well established and enshrined in relevant national and international guidelines (British Thoracic Society et al., 1993; National Heart, Lung and Blood Institute, 1995). The drug is delivered in close proximity to its intended site of action, resulting in rapid response. By-pass of the gastro-intestinal tract also eliminates absorption and metabolic variability associated with the route, permitting relative dose reduction and optimisation of the risk:benefit ratio.

Metered dose inhalers (MDIs) were first introduced into clinical practice for treatment of the symptoms of asthma and chronic obstructive pulmonary disease (COPD) in the 1950s by Riker Laboratories. The MDI is a convenient dose delivery system that is well liked by patients and prescribers and is less expensive than other respiratory delivery systems. About 80% of inhalation therapies in the world's largest patient

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populations are delivered by MDI (International Pharmaceutical Aerosol Consortium, 1997). In the UK alone, 39 million MDIs are used each year (Department of the Environment, Transport and the Regions, 1999) and annual world-wide production runs to about 500 million devices (Tansey, 1997a).

Despite this popularity, optimal dose delivery is dependent on patient technique and an ability to co-ordinate the actuation of the dose with inspiration of air into the lungs.

Incorrect use of MDIs has been reported to run to about 38% of users and, in spite of its obvious popularity, this mode of drug delivery may be unsuitable for some individuals (McFadden, 1995).

The alternatives are dry powder inhaler (DPI) and nebuliser which, like the MDI, enable delivery of a fraction of the equivalent oral dose of drug for the same therapeutic effect. Both of these devices have significant disadvantages that hinder wider utilisation. The dose delivered by DPI varies with age, gender, disease state and breathing cycle (Smith and Bernstein, 1996) and they are not suitable for all patient groups, especially very young children. Recent developments have seen the introduction of a variety of more user friendly multi-dose devices (Prime et al., 1997) and these have resulted in an increase in use of DPI products. However, the overall use of inhaled products has also grown and wider DPI use has not had a significant impact on MDI sales (Official Journal of the European Communities, 1998).

The nebuliser has not yet been produced in a convenient form for everyday use and current use is dominated by particular patient groups such as infants, patients with severe disease and those requiring higher doses of drug. Development of a portable reusable pocket-sized nebuliser system is underway (Hickey and Dunbar, 1997) but it is unlikely to be cost effective as a general replacement for MDIs.

In spite of the improved delivery efficiency of the respiratory route in comparison to oral administration, there are opportunities to improve drug targetting and reduce the dose still further. Less than 30% of the dose from a MDI or DPI reaches the lung and most of the remainder impacts on the oro-pharynx, with a smaller proportion retained within the mouthpiece of the actuator (Hickey and Dunbar, 1997). Some reformulated metered dose inhalers have been designed to improve the proportion of drug delivered into the lungs with consequent dose reduction compared to earlier products containing CFC propellants (Leach, 1998).

1.1. Respiratory disease

Incidence of asthma is estimated to be around 5–8% of the population in the developed world and the number of asthma sufferers world-wide amount to about 300 million people. Diagnosis of the disease is increasing at about 5% per year and it is the most frequently reported chronic condition among UK children. Asthma is responsible for the death of about 1700 people each year in the UK (International Pharmaceutical Aerosol Consortium, 1997; Official Journal of the European Communities, 1998).

The prevalence of chronic obstructive airways disease (COPD) has been estimated at around 8–15% of the general population and together with asthma, the two diseases comprise the third most common causes of death in the European Union (International Pharmaceutical Aerosol Consortium, 1997).

The demand for effective treatments for respiratory conditions therefore continues to grow into the new millennium. The range of drugs administered by inhalation is currently dominated by those intended for local pulmonary action. Advances in biotechnology have also stimulated interest in this route for drugs intended for systemic action. Respiratory delivery of acid or enzyme labile materials such as insulin, deoxyribonuclease, influenza vaccine and gene replacement therapy have been developed and the potential of this route for systemic treatment of other conditions remains to be fully realised.

1.2. Environment

Until 1995, all marketed MDIs contained chlorofluorocarbons (CFC) as the delivery propellant. CFC have been more extensively used for other

domestic and industrial purposes as a result of their chemical stability and low toxicity, however, concern over the possible detrimental effect of CFC to the ozone layer was first raised in the 1970s (Molina and Rowland, 1974). Since this time, the causal role of CFC in ozone layer thinning has gained support culminating in the signing of the Montreal Protocol on Substances That Deplete the Ozone Layer in 1987, which committed the signatory nations (now over 150) to cease production of CFC by 1996 (Montreal Protocol, 1987. Specific exemptions were granted for defined essential uses where there were no technologically or economically viable alternatives to CFCs and these included MDI production. Exemptions are issued on an annual basis and the pharmaceutical industry was faced with the prospect of diminishing, expensive supply and the possibility of being left behind by the first competitor to pioneer an equally popular alternative. In recognition of the popularity of this form of delivery, pharmaceutical aerosol manufacturers have committed large resources to the development of CFC-free MDI systems.

CFCs contribute both to the depletion of the ozone layer and to the greenhouse effect. The mechanism of ozone depletion is proposed to be via unbalancing of the stratospheric ozone formation and depletion equilibrium. Ozone is degraded to molecular oxygen plus free radical with the absorption of UV B radiation (Fig. 1).

The radicals formed may combine together to form molecular oxygen or with existing molecular

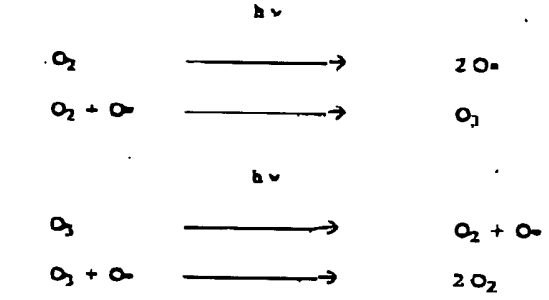


Fig. 1. Proposed stratospheric oxygen/ozone equilibrium (Noakes, 1995).

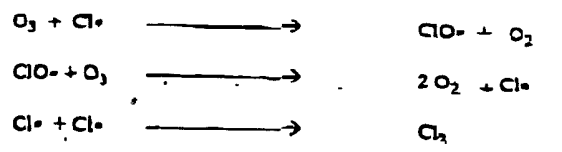


Fig. 2. Proposed halogen disruption of stratospheric oxygen/ozone equilibrium (Noakes, 1995)

oxygen to re-form ozone. CFC emissions pass directly into the upper atmosphere where they are retained until degraded by ultra-violet radiation releasing highly reactive chlorine radicals. Chlorine radicals catalyse the breakdown of ozone to molecular oxygen without the absorption of ultra-violet radiation or generation of oxygen radicals. One chlorine atom may be repeatedly recycled catalysing thousands of reactions prior to formation of molecular chlorine (Molina and Rowland, 1974) and more ultra-violet radiation is therefore transmitted to the surface of the Earth (Fig. 2).

Confirmation of stratospheric ozone depletion was first reported over the Antarctic in 1985 (Farman et al., 1985) and now occurs annually. Depletion of up to 40% of stratospheric ozone has been recorded in each year since 1995 over Northern Europe (Official Journal of the European Communities, 1998).

The consequences of ozone depletion for humans could manifest as increased incidence of skin cancer, eye damage and premature ageing of skin, while effects on the food chain and climate changes could adversely affect all life forms on the planet. The additional lifetime risk of skin cancer in children living in the UK today is predicted to increase by 4–10% if ozone depletion continues at the current rate (The Potential Effects of Ozone Depletion in the United Kingdom, 1996).

The problem is exacerbated by the stability of CFC in the upper atmosphere, with residence times of up to 200 years, leaving the burden of today's emissions with future generations.

1.3. The Montreal Protocol

The Montreal Protocol defines the circumstances permitting 'essential' use exemptions as;

Table 1
CFC approved by the Parties to the Montreal Protocol in the European Community, 1996–1999

Year	Tonnes of CFC
1996	7546
1997	6635
1998	5610
1999	5000

1. It is necessary for the health, safety or is crucial for the functioning of society (encompassing cultural and intellectual aspects).
2. There are no available technically and economically feasible alternatives or substitutes that are acceptable from the standpoint of environment and health.

Essential use applications are considered by the Technology and Economic Assessment Panel (TEAP) of the United Nations Environment Programme (UNEP) and criteria for essential use exemption have been defined as:

1. All economically feasible steps have been taken to minimise the essential use and any associated emissions of the controlled substance.
2. The controlled substance is not available in sufficient quantity and quality from existing stocks of banked or recycled controlled substances, also bearing in mind the developing countries' need for controlled substances.

Essential use status is considered every 2 years and requests for CFC for use in manufacture of MDIs are reviewed annually.

In the European Union, requests for CFCs for manufacture of MDIs are submitted to the Parties to the Montreal Protocol by the European Commission on behalf of Member States. Each manufacturer applies to the European Commission for authorisation to use a specified quantity of CFCs for the manufacture of MDIs. A management committee composed of representatives of the member states advises the European Commission on the quantities of CFCs to be allocated to each producer.

The quotas of CFC approved for use in the manufacture of MDIs in the European Community are indicated in Table 1.

This compares with over 400 000 tonnes of CFC produced for all industrial purposes in the USA alone in 1974 (Howard and Hanchett, 1975).

2. The metered dose inhaler

The device conventionally consists of five components which have an interdependent effect on drug delivery. These are; the drug substance, the canister, the propellant/excipient mixture, the metering valve and the actuator. The other significant factors on efficacy of drug delivery are patient technique and lung pathology.

Desirable functions of the MDI can be considered to be:

- Accurate and reproducible dosing.
- Efficient atomisation of the aerosol to deliver the drug to the required site.
- Retention of pressurised components.
- Protection of contents from external ingress.
- Convenient dimensions for user handling and portability.
- Multiple dose device ideally including an indicator of dose availability.
- Co-ordination of dose actuation with breath inspiration.
- Acceptable organoleptic properties.

Replacement of the propellant cannot be considered in isolation and implications for the MDI device are considered in the following discussion.

2.1. Aerosol propellants

In the absence of a new technology for respiratory drug delivery, the search for possible replacements for CFC for MDI was defined in terms of toxicity, flammability, chemical stability, physical properties and environmental compatibility. The template for these properties, with the exception of environmental suitability, were the existing MDI propellants, CFC 11, 12 and 114, which had been used safely and effectively for many years (Table 2). The candidates that emerged were hydrofluoroalkanes (HFA). Specifically, tetrafluoroethane (HFA 134a) and heptafluoropropane (HFA 227) were recognised as potentially suitable MDI propellants. These

Table 2
CFC and HFA propellants — nomenclature

Code name	Chemical name	Chemical structure
CFC 11	Trichlorofluoromethane	CCl_3F
CFC 12	Dichlorodi-fluoromethane	CCl_2F_2
CFC 114	Dichlorotetrafluoroethane	$C_2Cl_2F_4$
HFA 134a	Tetrafluoroethane	$C_2H_2F_4$
HFA 227	Heptafluoropropane	C_3HF_7

were non-flammable, non-ozone depleting, chemically stable propellants with suitable vapour pressures for MDI use.

Hydrofluoroalkanes contribute to the greenhouse effect but to a lesser extent than CFC (Table 3). It has been estimated that HFA from MDIs will contribute less than 0.1% of total world-wide greenhouse gas emission by 2005 (International Pharmaceutical Aerosol Consortium, 1997).

A further concern is the accumulation of trifluoroacetic acid, a breakdown product of HFA-134a, in wetland areas (Snell, 1995). The environmental effects of HFA are therefore not completely benign but the ozone depletion problem has demanded swift action. Development of HFA for MDI propellants is currently justified in balancing medical need against their environmental impact.

2.2. Propellant toxicity

Toxicity and environmental suitability of hydrofluoroalkanes were investigated initially in collaborative studies by chemical companies with an interest in their development. The Programme for Alternative Fluorocarbon Toxicity Testing (PAFT) commenced the toxicological and environmental screening of hydrofluoroalkanes and hydrochlorofluoroalkanes for industrial replacement of CFC propellants in 1987. This was followed in 1988 by the Alternative Fluorocarbons Environmental Acceptability Study (AFEAS) which investigated the environmental impact of potential CFC replacements. Further toxicology testing to meet the exacting requirements for medicinal products was conducted by the pharmaceutical industry. Collaborative International Pharmaceutical Consortia for Toxicology (IPACT) investigated the safety of these new propellants for respiratory delivery to humans in order to satisfy world-wide regulatory authorities. In Europe, the Committee for Proprietary Medicinal Products endorsed the suitability of HFA 134a and HFA 227 as propellants for administration into the lungs in its statements of 1994 and 1995, respectively(Committee for Proprietary Medicinal Products, 1994, 1995).

2.3. Physico-chemical properties of aerosol propellants

HFA and CFC propellants possess quite different physical and chemical properties (Table 4).

The vapour pressure of the MDI system determines the speed and rate of evaporation and, in turn, the aerosol droplet size and efficiency of deposition within the lung. High vapour pressure will provide small droplets due to rapid propellant evaporation but the velocity of plume discharge can result in large percentage of emitted dose impacting in the oro-pharynx (Polli et al., 1969;

Table 3
Environmental impact of MDI propellants (Smith, 1995)

Propellant	Ozone depletion potential	Atmospheric life (years)	Global warming potential[a]
CFC 11	1	60	1
CFC 12	1	125	3
CFC 114	0.7	200	3.9
HFA 134a	0	16	0.3
HFA 227	0	33	0.7

[a] Relative to CFC 11.

Table 4
Physico-chemical properties of MDI propellants (June and Ross, 1995; Tiwari et al., 1998a)

Propellant	Liquid density (g/ml)	Liquid viscosity (mPas)	BP (°C)	VP (psig at 20°C)
CFC 11	1.49	0.43	23.7	−1.8
CFC 12	1.33	0.22	−29.8	67.6
CFC 114	1.47	0.36	3.6	11.9
HFA 134a	1.21	0.22	−26.5	68.4
HFA 227	1.41	0.26*	−17.3	56.0

* Solvay Fluor und Derivate GmbH, Hanover, Germany.

Gonda, 1992; Harnor et al., 1993). Dalton's Law permits the total vapour pressure of a system to be determined by the sum of the partial pressures of its components and Raoult's Law provides for the calculation of the partial pressure of those components in the system. These have been used to design CFC propellant blends to achieve a suitable vapour pressure for lung deposition (Dalby et al., 1996).

The boiling points and vapour pressures of CFC and HFA propellants differ significantly (Table 4). The formulator of MDI using HFA propellants is potentially restrained by being unable to mix propellants with significantly differing vapour pressures to obtain desired lung deposition. That said, linear increase in vapour pressure of HFA-134a and HFA-227 blends with proportional increase in HFA-134a and compliance with Raoult's Law over a temperature ranges of 6–42°C have been reported (Williams and Liu, 1998), but there remains less flexibility to vary the system vapour pressure by blending different HFA propellants compared with the possibilities afforded using CFC propellants. The vapour pressure of HFA MDIs is likely to be higher unless other low volatility components such as ethanol are included.

The propellant boiling point impacts on the method of filling of the canisters. CFC 11 permitted preparation of the formulation as liquid at room temperature, filling and crimping the valve on to vial before adding the other propellants under pressure or low temperature via the valve. New processing routes for MDI containing HFA propellants have been required in order to liquefy the propellant (Smith, 1995).

The solvency properties of HFA propellants also differ from the CFC predecessors. Partial solubility of suspended drug substance in the dispersant may result in crystal growth, poor physical stability and unacceptable product performance. Surfactant solubility is very much reduced in HFAs with further implications for the physical stability of the system. The function of elastomeric components within valves and the profile of extractables released from these components are also influenced by the solvency properties of the propellant (Smith, 1995).

The capacity for CFC and HFA propellants to support microbial growth has been compared (Meier et al., 1996). Bactericidal properties of HFA 134a against *Staphylococcus aureus* are comparable to CFC blends whereas HFA 227 is bacteriostatic. *Bacillus subtilis* spores will survive in both CFC and HFA propellants. The authors conclude that testing of the microbial quality of MDIs containing HFA propellant should include a test of total viable aerobes in recognition of spore survival. They propose a tighter acceptance limit of ten bacteria per gram or millilitre as compared with the limit currently included in the European Pharmacopoeia (1997). They also argue that the Ph. Eur. test for absence of *S. aureus* is unnecessary as the organism does not survive in HFA 134a or proliferate in HFA 227.

2.4. Performance testing of reformulated MDIs

In reformulating products to replace the CFC MDIs, manufacturers have had to consider whether their objective should be therapeutic equivalence with the original CFC containing products or to improve the performance of the

new products. Characterisation of the aerodynamic particle size distribution of test and reference products is critical in this development. These data can be rationally used in the development and selection of products for further investigation of deposition in volunteers or patients and, where appropriate, pharmacokinetic studies. Ultimately pharmacodynamic and/or clinical studies will be required to demonstrate equivalence to existing CFC-MDI or, where there are changes to the dosage regimen, efficacy and safety of the reformulated product (Rogers and Ganderton, 1995).

2.5. Determination of aerodynamic particle size

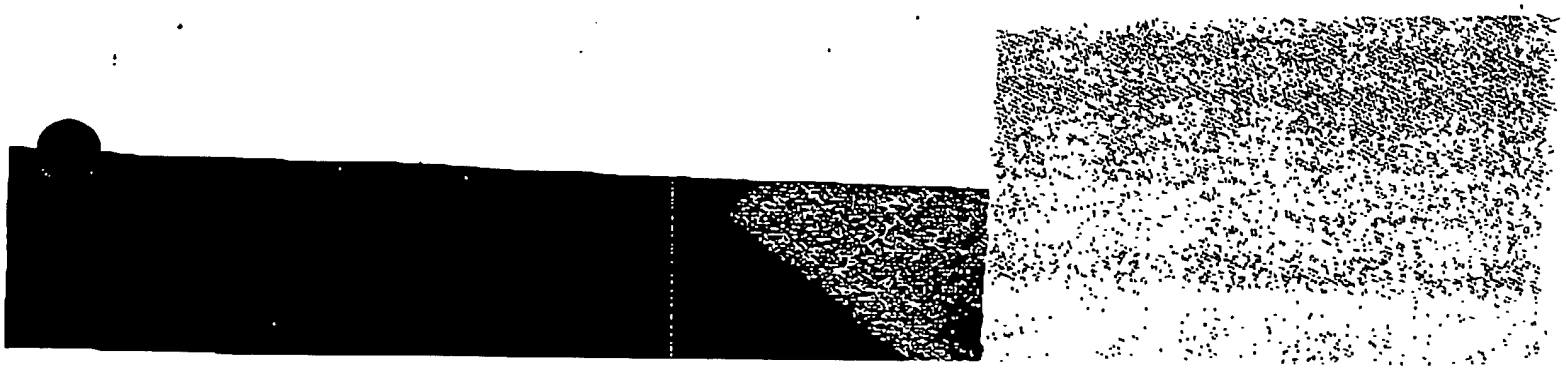
The aerodynamic size of the drug particle or droplet in the emitted aerosol determines the degree of deposition within the lung, the respirable (or fine particle) fraction and reflects the delivery efficiency of the system (Hickey, 1992). Deposition of a low percentage of the emitted dose within the lung leaves the residual deposited in the oro-pharynx, with increased probability of local and systemic side effects. The aerodynamic size is defined as the diameter of a sphere of unit density with the same settling velocity as the particle. This term takes account of particle size, density and shape, all of which influence the deposition pattern. Drug particle hygroscopicity and charge may also be significant and patient technique, inspiratory rate and volume and the disease state are further contributory variables (Padfield, 1987).

Aerosolised drug deposits in the lung by sedimentation, inertial impaction and Brownian motion (Hallworth, 1987). The momentum of large particles within the inspired airstream favours their early deposition in the bifurcating, narrowing airway system. Particles in excess of 10 μm will deposit in the oro-pharynx and are unlikely to reach the lungs. Those of diameter less than 1 μm deposit principally by Brownian motion. The tidal nature of respiration mitigates against significant drug deposition by Brownian motion and very small particles are exhaled before collision with the endothelium. The optimal size range for drug deposition is in the range 1–5 μm and has generally been defined as the respirable dose (Hickey, 1992). This terminology has been challenged on the basis that it infers a 1:1 correlation with the dose deposited in vivo and the alternative term, fine particle fraction (or dose), is proposed (Clark et al., 1998). It is also argued that an in vitro size range of 1–3 μm is more clinically relevant (Newhouse, 1998). By whatever name, this definition takes no account of site of deposition within the lung and the desirable aerodynamic size range for a product intended for systemic effect may therefore differ from another for local action on the smooth muscle within the lung.

Definition of a rapid, usable and predictive in vitro method is complicated by the dynamic nature of the aerosol with flash evaporation of propellant, decreasing droplet size and deceleration of the aerosol plume over distance, in addition to the complexity of the anatomy and physiology of the lung.

A number of different methods, based on different physical principles, can be used to characterise the aerosol size but results obtained from different methods will not be readily comparable (Tiwari et al., 1998a). Information on the real time dynamics of the aerosol plume is obtained by optical methods such as laser diffraction (Ranucci, 1992), holography (Gorman and Carroll, 1993), phase Doppler anemometry (Ranucci and Chen, 1993), time of flight spectroscopy (Niven, 1993) and right angle light scattering (Jager et al., 1993). These permit effects of formulation variables such as actuator and spacer design on the changing velocity and shape in the emitted plume but do not take account of respiratory tract tortuosity and the aerodynamic behaviour of the particles (Timsina et al., 1994).

Inertial impactors have been developed from instruments designed for microbial sampling of air to provide detailed information on the size, distribution and mass of the fine particle fraction of pharmaceutical aerosols. The sampling chamber of these devices is designed to approximate the human throat and the method of collection of the different size fractions of aerosol within the device bears similarities to the respiratory tract. Namely, that a particle suspended in a moving airstream will impact on an intervening surface when its inertia overcomes the drag forces tending



to retain it in the airstream (Milosovich, 1992). The largest particles impact on the initial stages and smaller particles are carried further through the instrument. An absolute filter is used to collect any fines. The collection medium may be liquid or a solid surface.

Particle size information is commonly expressed as median mass aerosol diameter (MMAD) and the spread of data as the geometric standard deviation (GSD). The distribution by mass or percentage of dose above the each pre-calibrated cut-off stage of the equipment provides useful comparative data between formulations.

The mass on each of the impactor stages does not correspond exactly with the ranges indicated by the manufacturers calibration and data may require inversion to ascertain the true size fractions (Cooper, 1993). Inversion is not usually conducted if the impactor is used for comparative studies of formulation or device variables but must be considered where studies are conducted using different impactor models and for prediction of deposition within the respiratory tract (Marple et al., 1998).

Data obtained can be variable within (Stein and Olson, 1997) and between (LeBelle et al., 1997) impactor models and will vary with sampling chamber dimensions (Aiache et al., 1993), carrier gas flow rate and single or multiple actuation of the device (Graham et al., 1995).

Less detailed information may be required for routine quality control after appropriate characterisation using the impactor method described above and on definition of product and manufacturing variables. Impinger methods have been included in the British Pharmacopoeia since 1988 for this purpose and have the advantage of simplicity but permit segregation of the aerosol into only two size categories.

The value of in vitro data in product development is dependent on how closely they predict the clinical efficacy of the product. Clinical response is dependent upon the dose and location of deposition relative to the target receptors. Bronchial and pulmonary circulation may also contribute to the delivery of the drug to its site of action. For example, cholinergic receptors are concentrated in the bronchi, while asthma inflammation is diffuse and the optimal aerodynamic characteristics may therefore differ for anticholinergic and steroid aerosols. Variation between patient populations must also be considered, for example in infants and children where aerosol deposition fficiency (for particles less than 3 μm) is less than adults (Chua et al., 1994). Deposition is further influenced by rate and volume of inspiration, hold time, airway calibre and variation in the lung and pulmonary parenchymal disease (Newhouse, 1998). The challenge for the in vitro method is considerable but correlations have been demonstrated between these methods and therapeutic effect for particular drugs (Meakin and Stroud, 1983; Padfield et al., 1983; Martonen and Katz, 1993). That said, no generally applicable correlation has been developed and in vitro methods alone are not yet acceptable as surrogates for clinical performance (Rogers and Ganderton, 1995).

2.6. Physical nature of the drug substance

Metered dose inhalers are formulated both as suspension and solution of drug in the propellant, depending on the solubility of the active substance in the propellant–excipient mixture. Suspensions have the advantage of chemical stability and delivery of greater mass per unit volume than solutions but have to be carefully formulated so that the physical stability is controlled throughout their lifetime. The potential for crystal growth, solvate formation or polymorph interconversion must be fully addressed early in the formulation development (Byron, 1992). The concentration of the suspension, method of micronisation and particle size distribution of micronised drug will influence the spray characteristics of the product (Gonda, 1985; Chan and Gonda, 1988; Ward and Schultz, 1995).

Aggregation of the finely divided solid phase with resultant sedimentation or creaming as a result of density differences between disperse phase and propellant, manifest as poor dose reproducibility and reduction in the fine particle fraction (Hallworth, 1987). Density differences between finely divided solid disperse phase and the liquid phase of the suspension should be min-

imised in order to promote the physical stability of the suspension and the resulting dose reproducibility.

Optimisation of physical stability and aerodynamic performance of a triamcinolone acetonide suspension MDI (including ethanol) by variation in the relative composition of a mixture of HFA 134a and 227 propellants has been recently demonstrated (Williams et al., 1998). Blending the propellants so that the density of the mixture approached that of the suspended drug improved dose uniformity. This blend also demonstrated the lowest median mass aerodynamic diameter and highest fine particle fraction and performance was maintained on short term storage.

Surfactants have been used to obtain the desired physical stability of the suspension and additionally function as lubricants for the metering valve. The choice of surfactant is limited by toxicological as well as physicochemical considerations, and those used in currently licensed CFC MDI formulations are oleic acid, sorbitan triethanoleate and soya derived lecithin. Surfactants prevent aggregation of the primary drug particles by adsorption onto the solid surface, with the predominant stabilising mechanism being steric repulsion between the projecting hydrophobic chains. Hydrofluoroalkanes are more polar than CFCs and have different and poorly characterised solvency properties (Byron et al., 1994). Solubilities of oleic acid, sorbitan trioleate and lecithin in HFA 134a are in the region 0.005–0.02% w/v (Byron et al., 1994; Dalby et al., 1996). CFC containing MDI formulations have required these surfactants at concentrations of between 0.1 and 2.0% w/w to stabilise the suspension and optimise the function of the metering valve (Atkins et al., 1992). New surfactants that are more soluble in HFA are under investigation. These include polyethylene glycol (PEG), propoxylated PEG and perfluoroalkonic acids but they will not be available until their safety has been demonstrated in chronic respiratory administration (Dalby et al., 1996). The lubricant function of surfactant is not required in newly developed valve systems and this has permitted development of commercial beclomethasone dipropionate (BDP) HFA MDIs without inclusion of surfactant (Snell, 1995). Another approach is to employ a co-solvent to solubilise surfactant in HFA and this may also overcome some of the manufacturing difficulties associated with the absence of a high boiling point replacement for CFC-11 (Tansey, 1997b). Low volatility co-solvents such as ethanol will decrease system vapour pressure and lower the fine particle fraction (Newman et al., 1982). Increasing the ethanol content in solution formulations of BDP in HFA134a decreased the fine particle fraction of BDP and increased actuator and impinger throat deposition (Steckel and Muller, 1998).

Solution formulations of drug in the propellant blend offer the theoretical advantage of improved dose uniformity compared to suspensions. Dose uniformity and aerodynamic size distributions of suspension formulations may vary with storage, orientation and the number of doses fired from the canister (Cyr et al., 1991; LeBelle et al., 1996). Spray characteristics of solution aerosols can also be manipulated by reduction in actuator orifice diameter and by increase in the length of the actuator mouthpiece to produce smaller droplet sizes and deaggregation of suspension particles (Evans et al., 1991; Ranucci et al., 1992; Vervaet and Byron, 1999) but suspensions have the tendency to clog a small diameter orifice.

Significantly greater lung deposition has been demonstrated using MDIs containing experimental solution aerosols compared to suspension aerosol in both healthy and asthmatic patients in scintigraphy studies (Sanders et al., 1997) but these advantages must be balanced against the potential disadvantage of poorer chemical stability of drugs formulated in solutions (Soine et al., 1992), the required concentration of surfactant to stabilise the active substance (Blondino and Byron, 1996) and the toxicological profile of the surfactant. Co-solvents and use of micellar systems to improve drug solubility in CFC propellants, have also been described (Evans and Farr, 1992) but reverse micelle formation has not been observed in HFA 134a (Blondino, 1995 in Vervaet and Byron, 1999).

Propellant solvency properties may necessitate manipulation of the form of the drug substance. Tzou et al., (1997) showed that physical instability

of salbutamol sulphate and base in HFA was correlated with drug solubility. Suspensions of base and sulphate containing oleic acid but without co-solvent had unacceptable physical stability with rapid flocculation and settling or creaming. These were improved by inclusion of ethanol. Resultant stable suspensions of salbutamol sulphate formed a three-dimension flocculated network and the particle size, by laser diffraction analysis, was maintained in the desired range of 2–3 μm over 12 months real time and accelerated testing. In contrast, suspensions of salbutamol base in the HFA/ethanol system were physically unstable as a result of crystal growth and agglomeration.

This strategy has been employed in the HFA containing formulations of Airomir™ and Ventolin Evohaler™, where salbutamol is incorporated in suspension as the sulphate while CFC MDIs contained suspensions of salbutamol base.

2.7. The metering valve

The metering valve is required to retain and protect the contents of the canister while delivering a fixed volume (usually 25–100 μl) of the formulation accurately and reproducibly throughout use by the patient. Appropriate valve design and manufacture are critical to dose uniformity and require thorough investigation in the development of the product. The volume of the metering chamber and the concentration of drug substance determine the emitted dose from the valve.

At rest, the chamber is open to the bulk liquid within the canister. During actuation, the inner seal closes and outer opens so that only the contents of the chamber are discharged under the vapour pressure of the propellant.

The metering valve assembly is crimped onto the aluminium can containing the liquid fill and the seals around this junction and within the valve prevent leakage of the canister contents and ingress of moisture. Differences in performance of valves developed for CFC MDIs when exposed to HFA are principally due to the effect of propellant on the elastomeric components of the valve (Williams, 1995).

The solvency properties of the propellant affect the degree of swelling (or shrinkage) of valve elastomers and therefore valve function as a barrier to moisture ingress, release of volatile contents and reproducible dosing (Tiwari et al., 1998b). The emitted dose may be further influenced by sorption of drug to valve components or canister (June et al., 1994).

The water content of the formulation is critical to the solvency of the system and can destabilise both solution and suspension formulations. Hydrolysis of susceptible drugs and reduction in system vapour pressure due to ingress of water into the canister are further concerns. (Atkins et al., 1992).

HFA propellants have a higher capacity for water than CFCs and higher water transmission rates into HFA formulations are observed through valves developed for CFC MDIs (Williams and Tcherevatchenkoff, 1997). In a study of a model suspension formulation in HFA propellant using ethanol as co-solvent but without surfactant, the particle size (MMAD) increased with increasing water content in the formulation, although the size distribution (GSD) and percent respirable fraction were not affected (Williams et al., 1997).

The effects of varying ethanol concentration in placebo HFA-134a formulations on the performance of commercial metering valves containing different elastomeric components have also been reported (Tiwari et al., 1998b). Problems of valve sticking and continuous emission occurred in formulations containing no ethanol, but were reduced with inclusion of 2% v/v ethanol, and completely eliminated in solutions containing 10% v/v of ethanol, prompting the conclusion that ethanol lubricates the valve. This was at the expense of increasing leak rates and valve swelling with increasing ethanol content.

Nitrile based rubbers are the most commonly used elastomers in CFC MDI valve systems (Williams, 1995). In addition to the elastomer, compositions of these rubbers typically include filler and curing agents and they could also contain accelerators, activators/retarders, antioxidants, plasticiser, processing aids and colourants (Paskiet, 1997).

Elastomer developments required for compatibility with HFA containing products have included; reduction in the content of elastomer in the device, improvements in the formulation of elastomers, reduction in components in the elastomer, use of alternative elastomer materials, removal of sources of polynuclear aromatics, avoidance of sulphur based curative processes and pre-cleaning /pre-extraction of elastomers (Howlett and Colwell, 1997).

The critical interdependence of MDI components to device functionality is evident in the preceding discussion and need to be fully considered in the design of the development programme, in order to achieve the desired performance characteristics in the reformulated product (Byron, 1992; Dalby et al., 1996).

3. Transition

The Parties to the Montreal Protocol required the preparation of national strategies for the transition to non-CFC containing MDIs by 31 January 1999. Continued availability of CFC for MDI manufacture is co-ordinated by the European Commission and the strategy for phase-out of CFCs in MDI was published in Official Journal of the European Communities in November 1998.

The stated principles guiding the phase out of CFCs in MDI are:

Principle 1: That all those involved will promote the transition to non-CFC alternatives.

Principle 2: That the health and safety of patients during the transition will be safeguarded.

Principle 3: That the nomination, approvals and licensing systems will be operated with efficiency, consistency and transparency.

The availability of CFC free products in the different member states may vary, dependent upon the national regulatory processes. The transition strategy for withdrawal of CFC based MDIs in the UK was published in 1999 by the Department of the Environment, Transport and the Regions. This attempts to co-ordinate the efforts of industry, health professionals and Government so that transition of patients to the new products is managed as effectively as possible.

When MDI products containing HFA propellants become available in European markets, the requirements for the 'essential use' exemption for CFC containing products will no longer be fulfilled. The European Commission has surveyed MDI manufacturers in order to predict the likely time course for CFC phase out. The best estimate is based around the intended dates of submission for Marketing Authorisations given by the producers (Table 5). It is envisaged that the transition to CFC-free MDI will be complete in the European Union by 2003. The UK strategy predicts completion of the transition one year earlier.

The strategies classify MDI products into the six categories based on the pharmacological activ-

Table 5
Expected time frame for loss of essential use status (Official Journal of the European Communities, 1998)

Drug	First stated filing date	Last stated filing date	Likely loss of essential use status*
Salbutamol	1996	2001	1998–1999
Terbutaline	2000	2004	2001–2002
Fenoterol	1998	2002	1999–2000
Beclomethasone	1996	2002	1999–2000
Budesonide	2000	2002	2001–2002
Cromoglycate	1998	1999	1999–2000
Ipratropium bromide	1999	2000	2000–2001

* Under the provisions of the strategy in all or some member states, provided that granting of Marketing Authorisations is not unduly delayed.

Table 6
Replacement of CFC containing MDIs with non-CFC alternatives (Official Journal of the European Communities, 1998)

Product	Number of alternatives	Number of producers
Category A: Short acting beta agonist brochodilators		
Salbutamol*	Two non-CFC salbutamol products	Two different producers
Terbutaline*, Clenbuterol, Fenoterol*, Bitolterol, Orcipreaaline, Procaterol, Reproterol, Carbuterol, Hexopreaaline, Pirbuterol	CFCs for all category A products will no longer be considered essential once there are two available alternative salbutamol products produced by two different producers PLUS one other product defined as necessary under this strategy. Therefore, these two products will be replaced by a minimum of three CFC-free inhalers (two salbutamol + one other)	
Category B: Inhaled steroids		
Beclomethasone*	Two non-CFC beclomethasone products	Two different producers
Dexamethasone, Flunisolide, Fluticasone*, Budesonide*, Triamcinolone	CFCs for all category B products will no longer be considered essential once there are available two alternative beclomethasone products produced by two different producers PLUS two other products containing different active substances defined as necessary under this strategy. Therefore these products will be replaced by a minimum of four CFC-free products (two beclomethasone + two others)	
Category C: Non steroidal antiinflammatories		
Cromoglicic Acid*, Nedocromil*	CFCs for both category C products will no longer be considered essential once there is one alternative CFC product available to replace either of the two current products. Therefore, the two CFC products will be replaced by a minimum of one CFC-free product, except where both products are considered essential	
Category D: Anticholinergic bronchodilators		
Ipratropium bromide Oxitropium bromide	CFCs for both category D products will no longer be considered essential once there is one alternative CFC product available to replace either of the two current products	
Category E: Long acting beta agonist bronchodilators		
Salmeterol*, Formoterol*	CFCs for both category E products will no longer be considered essential once there is one alternative CFC product available to replace either of the two current products. Therefore, the 2 CFC products will be replaced by a minimum of one CFC-free product, except where both products are considered essential	
Category F: Combination products		
	Combination products will be treated on a case by case basis. CFCs will no longer be considered essential once CFC products are available for each of the separate components in the combination	

* Denotes products deemed necessary under this strategy in one or more member states.

ity of the active substance. Phase out of CFC products will be conducted in a two step process and the criteria are summarised in Table 6. When sufficient products containing a particular drug meet the defined criteria, the essential use exclusion will be removed and CFC will no longer be permitted for manufacture of MDI products of that drug. For example, for salbutamol (which accounts for 90% of the European short acting beta agonist market), the strategy stipulates the

requirement for two alternative CFC-free products from different producers in an adequate range of doses. For products in categories C to E only one alternative is required. The next step occurs when sufficient drugs in a particular category are available, then essential use status will be removed for the entire category of products. The two systems will operate in parallel.

Categories A and B account for about 75% of CFC MDIs used in the UK and there are variety of brands and sources of active substance for the most widely used products. In category E, by contrast, salmeterol currently enjoys the exclusivity of new chemical entity and is marketed only by a single producer. At least one product in each of categories A to E, is also available as a dry powder inhaler.

The national strategy takes account of the prescribing preferences within the UK and considers the following drugs to be 'essential' so that phase out of CFC availability for particular categories will not be permitted until suitable non-CFC alternatives are available.

Category A:	Salbutamol and terbutaline
Category B:	Beclomethasone, budesonide and fluticasone
Category C:	Sodium cromoglycate
Category D:	Ipratropium bromide
Category E:	Salmeterol

Because of the prevalence of their use, at-least two different salbutamol products from different producers and one other CFC-free MDI containing terbutaline, must be available in an adequate range of doses prior to removal of essential status from category A. A similar situation arises with category B and beclomethasone dipropionate, but CFC-free MDIs containing fluticasone and budesonide are also required to be available prior to loss of essential status for this category.

Categories C, D and E require only one non-CFC product to be available and products stated to be essential in the UK in each of these categories are indicated above.

CFC use for combination products (category F) will no longer be considered essential once CFC free products containing each of the separate components, are available.

The strategy further stipulates requirements for production and distribution capacity of CFC-free MDIs, accommodation of distinct patient subgroups such as infants and the elderly, dose ranges to meet the needs of all patient groups and sufficient post marketing surveillance prior to removal of a particular essential use exemption.

It is notable that the only CFC-free BDP MDI currently licensed in the UK (Qvar™, 3M Healthcare), is not approved for use in children, although paediatric indications have been approved in other European Union countries.

Some products may not be reformulated or may lag the development of alternatives and patients using these products would be required to transfer to others within the same therapeutic category or to different delivery systems of the same drug, for example to a DPI.

It is envisaged that post marketing surveillance studies will take no more than 12 months from launch of a CFC-free MDI to highlight any safety issues and that the manufacture of further CFC-MDI, of that particular product, will be phased out over this time. This does not appear to take account of the different volume of use between different drug products and uptake by prescribers. During this time both CFC and CFC-free products would be available but it is acknowledged that availability of the original CFC products will vary greatly depending on stock rotation and it will require effective communication between prescribers, pharmacists and patients to ensure that the patient receives the intended product. Although it is acknowledged that CFC and CFC-free products are therapeutically equivalent, it is undesirable to switch back and forth between products containing the different propellants.

Withdrawal of essential use status for products or categories on fulfilment of these conditions will be administered by the European Commission, on advice from the competent authorities of Member states and other experts. This will, in turn be reflected in the subsequent European Commission application to the Parties to the Montreal protocol for CFCs to produce MDIs.

Manufacturers may continue to produce CFC MDI products within the UK (and Europe) for

export, particularly where there are significant cost implications for the developing world. The European Communication states that production for export will need to continue even after successful phase out in Europe but also that manufacturers should 'ensure that, wherever possible, patients relying on MDIs produced in Europe are given access to CFC-free inhalers and thereby benefit from the experience of transition in Europe'. One of the reasons given for the development of CFC-free MDIs was the threat of diminishing supply and increasing expense of CFC as essential use exemptions were removed and it is evident that this equally threatens the viability of manufacture of CFC MDIs for export only. This situation is currently being monitored by the Parties to the Montreal Protocol.

The success of this transition will be highly dependent on the awareness of healthcare professionals and patients of the issues of relevance to them and this is highlighted in both European and UK strategies. It is recognised that the level of awareness of healthcare professionals and patients about CFC-free MDIs is limited at present and that this will need to be improved as more become available in the marketplace. The development of active strategies to involve and inform patients will require involvement of Government, professional bodies, patient associations and manufacturers. Patients will notice differences in product appearance, taste, sound and impact in the oro-pharynx. They may be required to changeover to another drug or to a different delivery system or the dose of their usual drug may be changed. The potential for confusion is abundant but will be minimised by appropriate education and discussion with the users and it is recognised that this will also be an opportunity to revisit and reinforce information on good inhaler technique (Current Problems in Pharmacovigilance, 1999; Li Wan Po, 1999).

4. Re-formulated HFA-metered dose inhalers

CFC-free MDI products approved for marketing in the UK in September 1999 are listed in Table 7.

Devices containing salbutamol were, understandably, first to the market and Airomir™ (3M Healthcare, UK) was launched in the UK in 1995 followed by Ventolin Evohaler™(Allen and Hanburys, UK) in 1998. Beclomethasone dipropionate (BDP) was also launched in 1998 as Qvar (3M Healthcare, UK).

The approach to development of salbutamol and BDP was quite different. The template in the case of the salbutamol products was the in vitro aerodynamic profile of CFC salbutamol MDI and ultimately to demonstrate therapeutic equivalence to the CFC product in recognition of its 30 year history of safety and efficacy (Tansey, 1995). This clearly has the benefit that the patient can be changed over to the same dosage regimen. Although both HFA and CFC products are suspensions, the active is incorporated as the sulphate salt in reformulated products as compared to base in the original MDIs. The Airomir™ formulation

Table 7
HFA containing MDIs approved for marketing in the UK

Product	Active	Excipients	Date of approval
Airomir™ (3M Healthcare)	Salbutamol sulphate (120 μg)	Oleic acid Ethanol HFA 134a	March 1995
Airomir™Autohaler (3M Healthcare)	As above	As above	August 1997
Qvar ™(and Autohaler) (3M Healthcare)	Beclomethasone dipropionate (50 μg, 100 μg)	HFA 134a Ethanol	June 1998
Ventolin Evohaler™ (Allen & Hanburys)	Salbutamol sulphate (120 μg)	HFA 134a	July 1998

Table 8
Aerodynamic particle size of Qvar™ (3M Healthcare) and commercially available beclomethasone dipropionate CFC MDI (Leach et al., 1998)

Product	MMAD (μm)	Fine particle fraction[a] (%)
Qvar ™(3M Healthcare)	1.1	58
Beclomethasone dipropionate CFC MDI	3.5–4.0	21

[a] Less than 4.7 μm (Andersen Mark II Cascade Impactor).

contains oleic acid and overcomes problems of solvency in HFA-134a by inclusion of ethanol as a co-solvent. Ventolin-Evohaler™ contains only salbutamol sulphate suspended in HFA-134a without surfactant or co-solvent.

Development of Airomir™ has been well documented and it has been demonstrated to be equivalent to CFC salbutamol MDIs both in vitro and in the clinic (Tansey, 1997a,b).

The process of reformulation has also permitted some improvement to MDI performance. Variability in initial emitted doses of CFC MDIs has been reported, dependent on orientation and storage time (Cyr et al., 1991). The developments in valve technology required for Airomir™ show reproducible first dose after 14 days storage in any orientation (June and Ross, 1995). In practice, patients using intermittent 'reliever' MDI may titrate to effect, however it is clearly desirable to improve product dosing uniformity. CFC containing MDI also had problems reported with a 'tail off' effect where the dosing becomes erratic towards the end of the product life. Manufacturers routinely include fill volume overage so that dose delivery is reproducible over the 200 dose lifetime and the tail off effect occurs close to extinction, beyond the recommended 200 doses of the canister. The patient is not aware of the number of doses used or remaining because of the lack of a dose indicator. Developments in valve design required for Airomir™ showed reproducible dosing to extinction and a much more apparent end point for the patient (June and Ross, 1995). The benefit of a dose indicator for MDI remains unrealised.

Qvar™ was developed as a solution of BDP in HFA-134a and ethanol, in contrast to the original CFC containing products in which the same active was suspended in the propellant/excipient mixture. The drug formulation and developments in valve and actuator design have enabled reduction in the aerodynamic diameter of the Qvar™ aerosol and increase in the fine particle fraction (Tables 8 and 9). Data from one small in vitro study indicate that the aerosol emitted from the actuator is similar to that obtained using a spacer device (Table 9) (Purewal, 1998).

A small scintigraphic study of lung deposition of BDP in healthy volunteers demonstrated 55–60% deposition of the emitted dose from Qvar™ compared with only 4–7% for a formulation of CFC-BDP. Similar BDP deposition (56%) was

Table 9
Particle size distribution and fine particle mass of CFC-BDP (Becotide™ 100) and HFA-BDP (Qvar™) with and without a spacer, $n \geq 8$ (Purewal, 1998)

Product	Emitted dose μg (SD)	Dose <5 μm μg (SD)	Dose <2.5 μm μg (SD)	Throat μg (SD)
CFC-BDP	96.8 (4.0)	22.0 (1.9)	5.7 (0.7)	58.3 (3.9)
CFC-BDP+spacer[a]	51.8 (5.6)	34.9 (3.6)	7.7 (0.7)	1.1 (0.3)
HFA-BDP	77.2 (4.8)	48.7 (4.6)	44.6 (3.7)	27.2 (4.5)
HFA-BDP +Autohaler[b]	81.0 (3.7)	51.6 (7.5)	46.1 (5.8)	27.8 (5.0)
HFA-BDP+spacer[c]	48.8 (10.3)	47.3 (10.2)	42.7 (8.8)	1.0(0.4)

[a] Volumatic, Allen and Hanburys.
[b] Breath actuated inhaler, 3M Pharmaceuticals.
[c] Aerochamber, Trudell Medical.

also observed from the HFA-MDI in a further study in asthmatics (Leach et al., 1998). Increased lung deposition of the fine aerosol has permitted a dose reduction of 50% compared to CFC-BDP MDIs (Harrison et al., 1997) and therapeutic effect at half the corresponding dose of BDP CFC-MDI has been demonstrated in asthmatics, (Davies et al., 1998). The lower administered dose, would be expected to reduce inhaled steroid associated side effects such as hoarseness and cough. Adverse events associated with Qvar™ have been recently reviewed (Davies, 1998; Shaw, 1999). High doses of BDP from Qvar™ (800 μg daily) have less suppressant action on hypothalamic-pituitary-adrenal function than equivalent BDP doses (1500 μg daily) from CFC-MDI. However, incidence of dysphonia and cough is not significantly different for those treated with Qvar™ compared with CFC-BDP. This is despite scintigraphic data, which show that the fractional deposition in the oro-pharynx is reduced from over 90% with CFC-BDP to about 30% with HFA-BDP (Leach, 1998).

Another HFA-134a reformulated BDP MDI, Beclazone™, Norton (Waterford, Eire) has been approved for marketing in some European Union countries. In contrast to Qvar™, this product is claimed to be therapeutically equivalent with CFC-BDP on a 1:1 dose basis (Milanowski et al., 1999). Beclazone™ is also a solution of the steroid in propellant but in vitro aerodynamic sizing data and scintigraphic deposition studies are currently not available in published literature.

Availability of different HFA-BDP products which are therapeutically equivalent at different dose schedules further complicates the transition process and the need for effective communication between health professionals and patients is further evident (Health Service Circular 1998/180).

5. Conclusion

In response to the ban on production of CFCs, aerosol manufacturers have sought environmentally acceptable replacement propellants to permit continued manufacture of MDIs. This is understandable given MDI popularity and the limited time-scales imposed by the Montreal Protocol.

HFAs provide a safe alternative to CFCs as propellants in these devices but their physicochemical properties have required extensive redevelopment of the entire product. This has improved the understanding of the interdependency of the various elements within the device and provoked debate on in vitro functionality testing and its relevance to clinical efficacy. Products developed thus far have provided benefits of improved drug delivery, dose uniformity and a patient discernible end point at canister extinction.

HFAs are not environmentally neutral and contribute to hydrocarbon emissions, global warming and acid rain. Nevertheless, the contribution of HFAs to environmental damage is considered to be comparatively small and the health benefit of drugs formulated using HFAs currently outweighs the environmental concerns, but this may not continue indefinitely.

The technical challenge to reformulate MDIs has almost been achieved and the next challenge is the transition of patients from CFC-MDIs to the new products. Professionals and public alike require information and education about the need for the transition and the implications for their treatment. Patients will be faced with unfamiliar products that look, taste, sound and feel different to their usual regimens. Some dosage schedules may be changed and some patients may be transferred to different active substances or to different drug delivery systems. Metered dose inhalers are used by many millions of patients and early identification of safety issues through effective pharmacovigilance is essential. Maintenance of disease control is paramount and the management of a seamless transition is the challenge for professionals, industry and Government.

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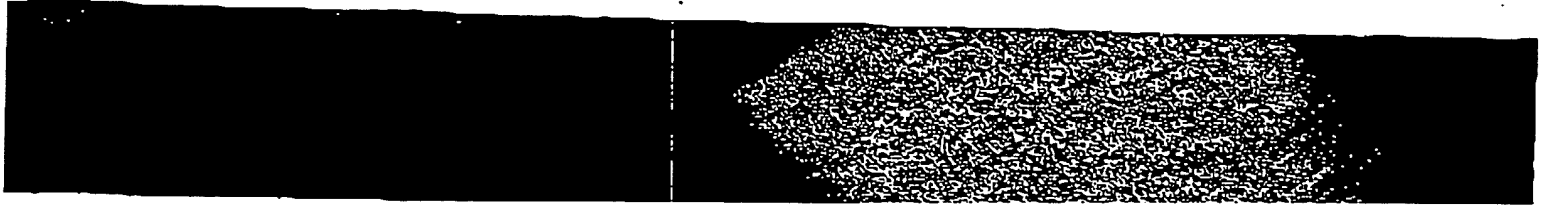

EXHIBIT B

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Research paper

Application of co-grinding to formulate a model pMDI suspension

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Abstract

The objective of this study was to investigate the effect of co-grinding the model drug, triamcinolone acetonide (TAA), with a polymeric surfactant on the in vitro performance of a model pMDI suspension system. The physicochemical properties of TAA after co-grinding with the surfactant, Pluronic F77®, were determined by laser light diffraction, helium pycnometry and equilibrium solubility measurements. TAA-surfactant interaction was investigated by differential scanning calorimetry and Fourier transform infrared spectroscopy (FTIR). The suspension characteristics of pMDI formulations prepared with co-ground TAA and surfactant were investigated by determining their in situ sedimentation, rheological profiles and vapor pressure. The performance characteristics of the pMDI formulations were determined by cascade impaction and dose delivery through-the-valve (DTV) measurements. It was found that the presence of Pluronic F77® decreased the solubility of TAA in the propellant medium. Co-grinding TAA particles with Pluronic F77® influenced the particle size distribution, sedimentation and flocculation characteristics of the pMDI suspension formulation. The addition of Pluronic F77® decreased the viscosity of the pMDI formulation. Formulating the suspension pMDI system with co-ground TAA and Pluronic F77® decreased the mass median aerodynamic diameter (MMAD) of the emitted aerosol and increased the percent respirable fraction (%RF). The co-ground TAA and Pluronic F77® pMDI suspension formulation exhibited greater physical stability which was due to the influence of the co-grinding technique on the physicochemical properties of the TAA particle surface and the propellant dispersion medium. The changes induced by co-grinding with Pluronic F77® improved the performance characteristics of a pMDI suspension formulation by stabilizing the suspension and influencing the flocculation characteristics. Co-grinding is a process which may be useful when developing new pMDI systems containing HFA propellants. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Co-grinding; Pressurized metered dose inhaler; Suspension; Co-polymer; Surfactant; Pluronic F77®

1. Introduction

Due to their reported depletion of ozone in the atmosphere, chlorofluorocarbon (CFC) propellants which are used in pressurized metered dose inhalers (pMDI), are being phased out and replaced by hydrofluoroalkane (HFA) propellants [1]. Differences in polarity between the CFC and the HFA propellants have presented significant obstacles in the development of new pMDI systems [2,3]. Drugs which were not soluble in the CFC propellants and were formulated as suspension pMDI systems may be appreciably soluble in the HFA propellants. Although the surfactant, oleic acid, was found to be soluble in P134a, other surfactants such as lecithin and sorbitan trioleate are not soluble in HFA media [2]. Reports of the influence of HFA propellants, P134a and P227, on the vapor pressure, density and aerodynamic particle size distribution of model pMDI suspension systems have indicated a need for further investigation [3].

Some researchers have focused on identifying and investigating new surfactants for the dispersion and stabilization of HFA based pMDI formulations. A recent US patent describes the use of polyglycolyzed glycerides in aerosol drug formulations containing P134a and P227 for preventing unwanted aggregation of a suspended medicament [4]. Another US patent documents the use of surfactants having a hydrophilic-lipophilic balance (HLB) greater than 9.6 in pMDI formulations containing P227 [5]. Polymeric surfactants such as the block copolymers of ethylene oxide (EO) and propylene oxide (PO), may also be suitable for dispersion and stabilization of HFA based pMDI formulations. The block copolymers of EO and PO, also referred to as poloxamers, behave differently from nonionic hydrocarbon lipophiles. Their HLB depends on the ratio of the number of EO groups in the hydrophilic chain and the number of PO groups in the hydrophobic chain [6]. Co-grinding water insoluble drugs with various types of water soluble poly-

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mers and surfactants has been utilized to enhance drug dissolution and solubility by improving the wetting of drug particles [7]. Changes in drug particle size and the molecular interactions between the drug and polymeric surfactant may affect the enthalpy of the solid and influence the dissolution properties of the drug [8]. Co-grinding solid drug particles with these polymeric surfactants may influence suspension characteristics and drug solubilization properties in HFA propellants. Pluronic F77® is a solid at 20°C, has a molecular weight of 6,600 and an HLB of 25 [9]. Although it is highly hydrophilic, the solubility in a 1:1 (w/w) P134a and P227 propellant mixture was found to be greater than 0.1% (w/w). Therefore Pluronic F77® was chosen as a model polymeric surfactant for co-grinding with the model drug, TAA.

The objectives of this study were to investigate the effect of co-grinding the model drug, triamcinolone acetonide (TAA), with a polymeric surfactant on the physicochemical properties of TAA and to determine the influence on the in vitro performance of a model pMDI suspension system.

2. Materials and methods

2.1. Materials

The hydrofluoroalkane propellants used were: Dymel Ultrapure P134a (P134a; 1,1,1,2-tetrafluoroethane; DuPont Chemicals; Wilmington, DE) and Solkane 227 Pharma (P227; 1,1,1,2,3,3,3-heptafluoropropane; Solvay Fluorides, Greenwich, CT). Methanol (EM Science; Gibbstown, NJ) and the model drug, Triamcinolone Acetonide USP (The Upjohn Co.; Kalamazoo, MI) was used. The surfactant investigated was the Pluronic grade F77® Prill (BASF; Mount Olive, NJ).

2.2. Co-grinding procedure

A 10 g aliquot of TAA and a 10 g aliquot of 3:1 (w/w) TAA and Pluronic F77® were ground in a porcelain centrifugal ball mill grinding apparatus (US Stoneware, Inc.; East Palestine, OH). The ball mill apparatus consisted of a 237 ml chamber and 20 zirconia balls measuring 3/8 inch in diameter. Test samples were ground at 20 rev./min for 6 h at 24°C and 55% RH. Also, a 10 g aliquot of a 3:1 (w/w) TAA and Pluronic F77® physical mixture was prepared by geometric dilution using a glass mortar and pestle.

2.3. Preparation of suspension pMDI formulations

Suspension pMDI formulations were prepared by measuring 30 mg of control TAA (not subjected to grinding), ground TAA, and 40 mg of co-ground or physical mixture of 3:1 (w/w) TAA and Pluronic F77® blends into aluminum cans (Cebal S.A.; Bellegarde, France) crimped with 75 μl metering chamber valves (Model DF10; Valois of America; Greenwich, CT). The canisters were filled with 5 g of P134a and 5 g of P227 using a Pamasol crimping and propellant filling unit (Models P2005 and P2008; Pamasol Willi Mader AG; Pfaffikon, Switzerland). The suspension pMDI formulations were prepared in triplicate.

2.4. Dose delivery through-the-valve

The dose delivery through-the-valve (DDV) was determined by collecting the contents of the metering chamber emitted for each pMDI formulation in a dosage unit sampling tube equipped with a firing adapter (26.6 × 37.7 × 103.2 mm; 50 ml volume, Jade Corporation; Huntingdon Valley, PA). Three actuations from each pMDI formulation were collected. Methanol was added to the dosage unit and the amount of drug emitted per actuation was determined by HPLC [10]. A Shimadzu Liquid Chromatography system (Model 6A with CLASS-VP automated software system; Shimadzu Inc., Columbia, MD) was used. The mobile phase was composed of phosphate buffer (pH = 3.0)/methanol (63:37). A 150 × 4.6 mm Inertsil 5μ ODS 2 column (MetaChem Technologies Inc., Torrance, CA) and a Shimadzu UV detector operating at 240 nm were employed. The flow rate was controlled at 1.5 ml/min. The HPLC analysis met all system suitability requirements for precision and accuracy.

2.5. Aerodynamic particle size distribution

An 8-stage cascade impactor (Andersen I ACFM Non-Viable 8-Stage Cascade Impactor with a USP Induction Port, Mark II, Graseby-Andersen; Smyrna, GE) was used to determine the aerodynamic particle size distribution of the dose emitted from the pMDI systems investigated. Twenty-five actuations were collected for each cascade impaction determination. Glass fiber filter paper (Graseby–Andersen) was used as the collection substrate. Methanol was used to solubilize TAA from the glass filter substrate. The mass of TAA deposited on each stage of the impactor, the induction port and the actuator was determined by HPLC [10]. The mass median aerodynamic diameter (MMAD) was determined from a plot of the cumulative percent mass of drug versus the particle size less than stated on log-probability paper. The percent respirable fraction (%RF) was calculated as the mass fraction of drug emitted from the test pMDI system which was less than 4.7 μm.

2.6. In situ sedimentation and velocity

The method used to determine the in situ sedimentation of the test pMDI suspension formulations was adopted from a method recently described by Miller et al. [11]. Briefly, a dosage unit sampling tube equipped with a firing adapter was used to collect the dose of drug emitted from the valve. Each test pMDI system was shaken manually, then the valve stem was immediately depressed and held down for 0, 5, 10 and 15 s into a waste sampling tube. As a result, the meter-

Table 1
The aerodynamic particle size distribution and DDV of test pMDI systems after storage for five days at 25°C. Standard deviations (SD) are given in parenthesis

PMDI formulation	MMAD (μm)	SD	GSD	%RF	SD	DDV (μg)	SD
Ground TAA	4.6	(0.29)	2.2	23.5	(7.13)	170.8	(16.31)
TAA/F77 physical mixture	3.5	(0.17)	2.0	30.9	(2.65)	184.3	(8.108)
TAA/F77 co-ground	2.7	(0.26)	2.6	33.6	(1.60)	197.8	(24.73)

ing chamber of the valve was loaded with formulation at the designated loading interval. The drug content of the loaded metering chamber was collected by actuating once into separate dosage unit sampling tubes corresponding to each time interval. The drug collected in the sampling tube was dissolved in methanol and analyzed by HPLC [10]. The theoretical sedimentation velocity of the suspension pMDI formulations was calculated using the Stokes law equation and their corresponding experimentally determined values for density, particle size and viscosity [12].

2.7. Helium pycnometry

An AccuPyc 1330 (Micrometrics, Inc.; Norcross, GA) was used to determine the true density of ground TAA, co-ground TAA and Pluronic F77® and the TAA and Pluronic F77® physical mixture ($n = 5$).

2.8. Vapor pressure

The vapor pressure of the test pMDI formulations was determined using a head pressure test gauge (Model P700; Pamasol Willi Mader AG; Pfaffikon, Switzerland). The vapor pressure of the pMDI systems at 25°C was recorded by coupling the test gauge to the valve stem and opening the pMDI system by depressing down on the valve ($n = 3$).

2.9. Particle size distribution

The particle size distribution of control TAA, ground TAA, co-ground TAA and Pluronic F77® and the physical mixture of Pluronic F77® and TAA were measured with a Shimadzu SALD-1100 laser light diffraction particle size analyzer (Shimadzu Inc., Columbia, MD). The median diameter (M50) was determined at the 50th percentile of particles undersized. The polydispersity was given by a span index which was calculated by (M90 - M50)/M50 where M90 is the particle diameter determined at the 90th percentile of particles undersized [13]. The co-ground and physical mixture were washed with cold water to remove the surfactant prior to measurement. Dispersions of washed TAA were prepared in an aqueous 0.01% Tween 80 solution utilizing a water bath with sonication ($n = 3$).

2.10. Triamcinolone acetonide solubility

The equilibrium solubility of TAA in purified water and in a 1:1 (w/w) P134a and P227 propellant blend was determined after storage for five days at 25°C. To determine the equilibrium solubility in purified water, 30 mg of TAA and 40 mg of 3:1 (w/w) TAA and Pluronic F77® blends were dispersed in 10 ml water and placed in an automatic shaker. The test samples were filtered and the concentration of TAA in the filtrate was measured by HPLC analysis [10]. A similar method to that described by Dalby et al. was used to determine the solubility of TAA in liquid propellant [14]. Briefly, a donor canister containing the test pMDI formulation was crimped with a continuous spray valve then stored inverted in an automatic shaker. After five days at 25°C, the donor pMDI systems were coupled to an empty receiver canister by a modified Gelman filtration apparatus (25 mm In-line Delrin® Filter Holder; Pall Gelman Sciences; Ann Arbor, MI). The soluble contents of the test pMDI formulations were passed through the filter into the empty receiver canister, and the concentration of TAA in solution was measured by HPLC analysis [10].

2.11. Fourier-transform infrared spectrophotometry

FTIR chromatographs were obtained using a Nicolet Magna-IR® Spectrometer 550 (Nicolet Instrument Corporation; Madison, WI) and Omnic 1.20 FT-IR data acquisition software. Test samples were mixed with potassium bromide, FTIR grade (Aldrich Chemical Co.; Milwaukee, WI) and packed in a sample holder to make pellets. The percent transmittance spectral data was collected over a wavenumber range of 500–4000 cm^{-1}.

2.12. Modulated differential scanning calorimetry

Differential scanning calorimetry (DSC) was performed with a DSC 2920 Modulated DSC and Thermal Analyst 2000 software (TA Instruments, New Castle, DE). An aliquot of 5.0 mg of each test sample was hermetically sealed in aluminum pans. An empty sealed pan was used as a reference. The heating program was conducted using the modulated setting at 10°C/min over a range of 20–320°C ($n = 3$). Temperature oscillation rate was 0.32°C every 60 s.

2.13. Rheology of pMDI formulations

An in-line viscometer (Model SPC-371; Cambridge Applied Systems, Inc., Medford, MA) was employed to perform the viscosity measurements. The viscometer was fitted with a continuous flow valve at the inlet and a metered flow valve so that the sampling chamber could be completely filled and sealed with the pMDI test samples. The viscometer was calibrated with a piston suitable for viscosity measurements in the range 0.2–2.0 cp. The temperature of

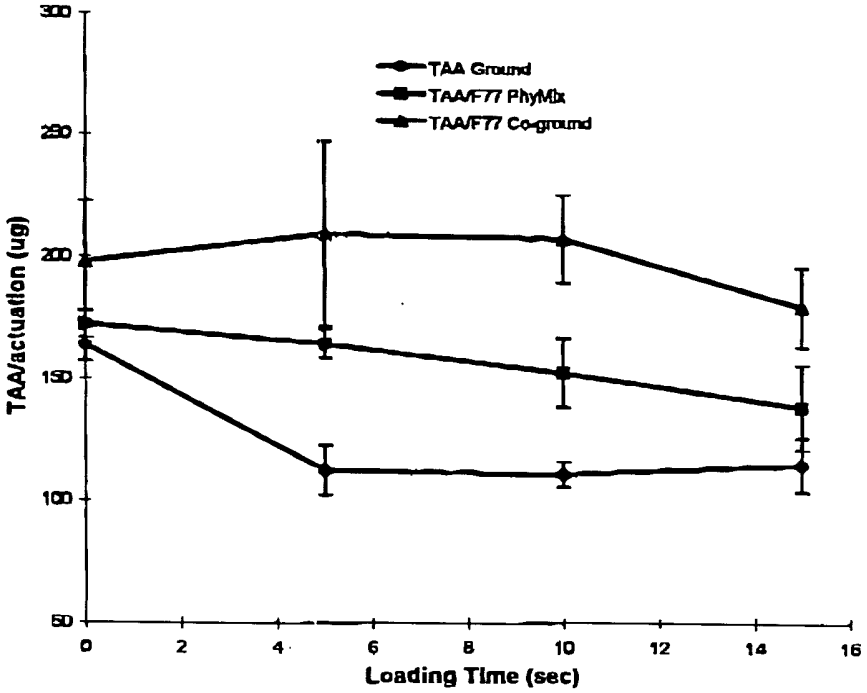

Fig. 1. Sedimentation properties of ground TAA, co-ground and TAA and Pluronic F77 physical mixture pMDI suspension formulations after storage for five days at 25°C.

the pMDI test samples was controlled at 25°C during the experiment with a refrigerated circulation bath. The viscosity measurements were determined on replicates of five samples.

3. Results

3.1. Mass median aerodynamic diameter and %RF of pMDI Formulations

The effect of co-grinding TAA particles with Pluronic F77® on the aerodynamic particle size distribution of the emitted aerosol is described in Table 1. The MMAD of the aerosol prepared from a pMDI formulation of ground TAA was 4.6 μm. The MMAD of the aerosol prepared from a pMDI formulation of co-ground TAA and Pluronic F77® was 2.7 μm. The MMAD of the aerosol generated from a TAA and Pluronic F77® physical mixture pMDI formulation was 3.5 μm. The %RF of the co-ground TAA and Pluronic F77® pMDI formulation was 33.6%, and the %RF of the pMDI formulation prepared with the physical mixture of TAA and Pluronic F77® was 30.9%.

3.2. Dose delivery through-the-valve of pMDI formulations

Matching the density of the dispersion medium and the dispersed phase will reduce the tendency toward creaming or settling of a suspension formulation [15]. Therefore a 1:1 (w/w) P134a and P227 propellant blend was chosen as the dispersion medium for the pMDI formulations since the calculated liquid density of the propellant blend (1.35 g/ml) was similar to the density of the test samples determined experimentally by helium pycnometry. However the pMDI formulations prepared in this study were observed to settle in the 1:1 (w/w) P134a and P227 propellant system. The DDV of a pMDI is a measurement of the amount of drug that is loaded into and expelled from the metering chamber immediately after actuation and may be influenced by the sedimentation characteristics of the formulation. As shown in Table 1, each test pMDI formulation emitted less than the theoretical amount of TAA per actuation (300 μg). However the magnitude of the DDV found for the co-ground TAA and Pluronic F77® pMDI formulation was most similar to the theoretical value.

3.3. In situ sedimentation of pMDI formulations

Information about the physical stability of the suspension pMDI formulations may be obtained by measuring the amount of drug that is loaded into the metering chamber after allowing designated time intervals for the suspension to equilibrate after shaking. Fig. 1 describes the in situ sedimentation of the test pMDI formulations by measuring the amount of TAA that was loaded into the metering chamber after allowing 0, 5, 10 and 15 s for the suspension to equilibrate with the metering chamber held in the open

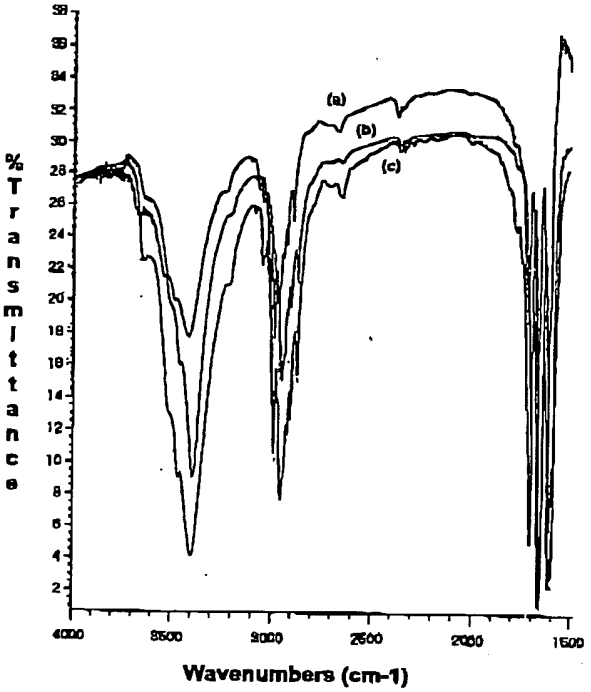

Fig. 2. FTIR chromatograms of: (a) ground TAA, (b) co-ground TAA and Pluronic F77 and (c) TAA and Pluronic F77 physical mixture.

position after shaking. It was found that the concentration of TAA emitted from the valve was influenced by the time allowed for loading the metering chamber. The concentration of TAA loaded into the metering chamber from the ground TAA pMDI formulation decreased after 5 s then did not change for 15 s. A decreasing trend was found for the concentration of TAA loaded and emitted by the TAA and Pluronic F77® physical mixture pMDI during the 15 s allowed for loading the metering chamber. Although not significantly different, the concentration of TAA loaded and emitted by the co-ground TAA and Pluronic F77® pMDI formulation after 5 and 10 s was slightly greater than at 0 s. After allowing 15 s for loading the metering chamber the TAA concentration emitted by the co-ground TAA and Pluronic F77® pMDI formulation decreased.

3.4. Density of dispersed phase

The density of the dispersed phase was not influenced by co-grinding process. The average density of the test samples was 1.33 ± 0.14 g/ml.

3.5. Vapor pressure of pMDI formulations

The addition of co-solvents and surfactants has been found to affect the vapor pressure of pMDI formulations [16]. However the addition of Pluronic F77® did not influence the vapor pressure of a 1:1 (w/w) P134a and P227 propellant mixture. Also the vapor pressure of the pMDI formulation prepared from co-ground TAA and Pluronic F77® was not significantly different from the pMDI formulation prepared with a physical mixture of TAA and Pluronic F77®. The average vapor pressure of the pMDI formulations was 89.1 ± 0.623 psi. The vapor pressure of the pMDI formulations was found to deviate slightly from the theoretical vapor pressure of the propellant blend which was calculated by Raoult's law to be 87.1 psi.

3.6. Triamcinolone acetonide -surfactant interaction

Hydrogen bonding between TAA and Pluronic F77® was shown by FTIR spectrophotometry. The FTIR chromatograms in Fig. 2 show an increased peak corresponding to the —OH stretch between 3650 and 3200 cm^{-1} and the —CH stretch in the range 3000–2840 cm^{-1}. Interactions such as hydrogen bonding between TAA and Pluronic F77® may be indicated by an increase in the parameters of melting point, heat capacity and heat of fusion [19]. Thermal graphs of TAA and blends of TAA and Pluronic F77® are presented in Fig. 3a–d. The melting point of control TAA was found to be 279.4°C and was not significantly different from ground TAA ($P < 0.05$). The DSC thermograms reveal an increase in the melting point of TAA in the presence of Pluronic F77®. The melting point of the co-ground and physical mixture of TAA and Pluronic F77® was found to be 291.8 and 294.3°C, respectively. Also an increase in the heat of fusion, ΔH_{fus}, was found by combining Pluronic F77® with TAA. The ΔH_{fus} increased from 46.3 to 66.5 J/g for the physical mixture and to 69.5 J/g for the co-ground mixture of TAA and Pluronic F77®.

Table 2
The viscosity of control samples and test pMDI formulations after storage for five days at 25°C

pMDI formulation	Average viscosity at 25°C (cp)	Standard deviation	% Relative standard deviation
100% P134a	0.202	0.005	2.56
100% P227	0.245	0.002	0.789
1:1 (w/w) P134a/P227	0.215	0.001	0.529
0.1% (w/w) Pluronic F77	0.239	0.007	2.97
0.3% (w/w) TAA	0.389	0.016	4.21
3:1 (w/w) Physical-mixture	0.280	0.005	1.60
3:1 (w/w) Co-ground	0.265	0.003	1.15

Table 3
The particle size distributions of test samples after co-grinding and after storage of test pMDI formulations for five days at 25°C

Test sample description	After co-grinding		After formulation	
	M50 (μm)	Span index	M50 (μm)	Span index
Control TAA	4.0	1.6	NA	NA
Ground TAA	4.5	1.6	6.4	2.9
TAA/F77 Physical mixture	5.8	1.0	4.7	2.0
TAA/F77 Co-ground	5.3	1.1	3.7	2.6

3.7. Rheology of pMDI formulations

Polymers may be excellent viscosity modifiers and therefore the impact of the selected poloxamer on the viscosity of the 1:1 (w/w) P134a and P227 propellant system was measured. The results of these measurements are described in Table 2. The average viscosities of P134a and P227 were found to be 0.202 ± 0.005 and 0.245 ± 0.002 cp, respectively. The average viscosity of a 1:1 (w/w) blend of P134a and P227 was found to be 0.215 ± 0.001 cp. The addition of Pluronic F77® added directly into propellant, at a concentration of 0.1% (w/w), was found to increase the viscosity of the propellant blend to 0.239 ± 0.007 cp. Dispersion of ground TAA particles at a concentration of 0.3% (w/w) in the propellant also increased the viscosity to 0.389 ± 0.016 cp. The 3:1 (w/w) combination of TAA and Pluronic F77® increased the viscosity of the 1:1 (w/w) P134a and P227 blend to 0.280 ± 0.005 cp for the physical mixture and to 0.265 ± 0.003 cp for the co-ground pMDI system.

3.8. Particle size distribution of triamcinolone acetonide

The particle size distribution of the test samples was determined prior to formulating in a pMDI and is presented in Table 3. Grinding did not significantly influence the M50 of TAA, however co-grinding TAA with Pluronic F77® increased the M50 to 5.3 μm and the physical mixture was further increased to 5.8 μm ($P < 0.05$). The dispersity of the particle size distribution was not influenced by grinding but the span index was found to decrease when Pluronic F77® was combined with TAA by co-grinding and by physical mixture. The particle size distribution of the test samples recovered by filtration after formulation in a pMDI system using a 1:1 (w/w) P134a and P227 propellant blend is also described in Table 3. The M50 of the ground TAA pMDI

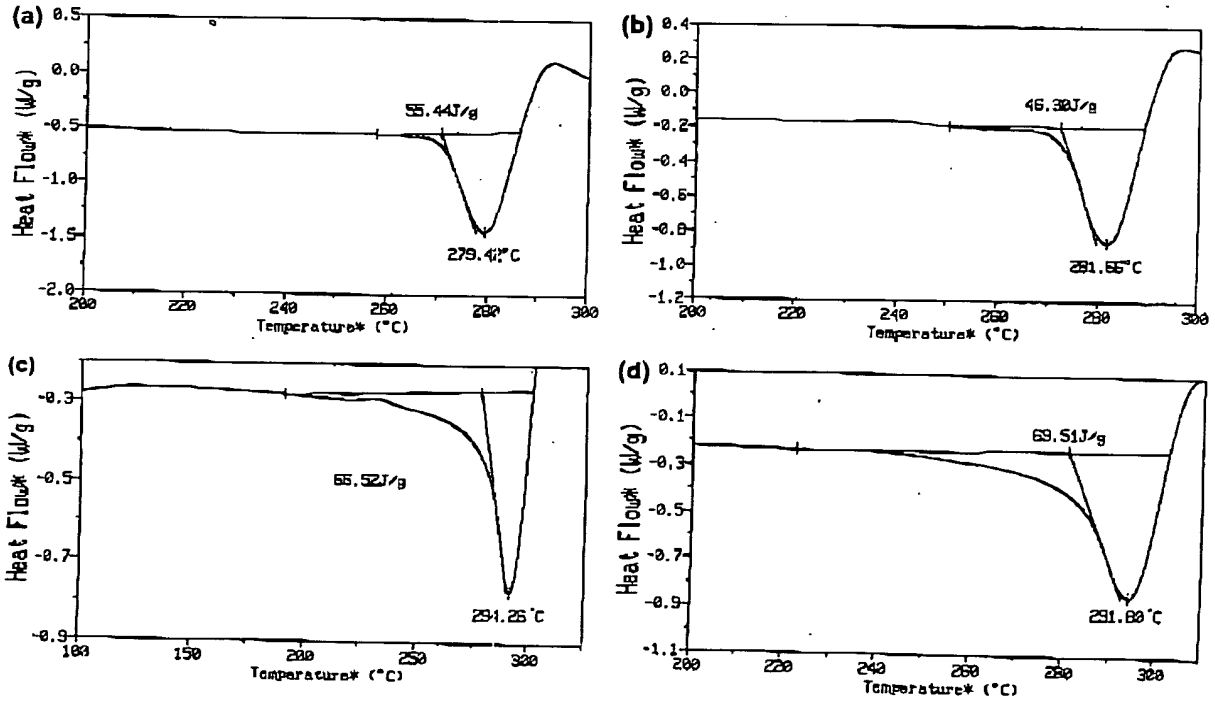

Fig. 3. DSC thermograms of: (a) control TAA, (b) ground TAA, (c) co-ground TAA and Pluronic F77 and (d) TAA and Pluronic F77 physical mixture.

Table 4
The solubility of TAA in water and in a 1:1 (w/w) P134a/P227 propellant blend after five days at 25°C. Standard deviations (SD) are given in parenthesis

Sample description	Solubility in water (μg/ml)	SD	Solubility in propellant (μg/ml)	SD
Control TAA	17.0	(0.333)	71.7	(6.47)
Ground TAA	18.0	(0.400)	79.6	(6.11)
TAA/F77 Physical mixture	20.9	(0.350)	42.2	(6.30)
TAA/F77 Co-ground	19.5	(0.957)	57.2	(7.05)

formulation was found to be 6.4 μm which is larger than the M50 of the ground TAA before dispersion and storage in propellant. The addition of Pluronic F77® as a physical mixture decreased the M50 of the ground TAA suspension pMDI formulation to 4.7 μm ($P < 0.05$). Co-grinding TAA with Pluronic F77® further decreased the M50 of the pMDI formulation to 3.7 μm ($P < 0.05$). The dispersity of the particle size distribution increased due to formulation and storage in the propellant system. The span index of ground TAA increased from 1.6 before formulation and storage to 2.9 after formulation and storage and the span index was found to increase two times when Pluronic F77® was incorporated ($P < 0.05$).

3.9. Triamcinolone acetonide solubility

The solubility of TAA in water and in a 1:1 (w/w) P134a and P227 propellant blend is shown in Table 4. Grinding did not significantly influence the solubility of TAA in water since the solubility of control TAA and ground TAA in water was 17.0 and 18.0 μg/ml, respectively ($P > 0.05$). However, the addition of Pluronic F77 as a physical mixture and by co-grinding significantly increased the solubility of TAA in water ($P < 0.05$) to 20.9 and 19.5 μg/ml, respectively. The solubility of the TAA and the TAA and Pluronic F77® blends in the non-polar propellant medium was significantly greater than in water. The solubility of control TAA in a 1:1 (w/w) P134a and P227 was found to be 71.7 μg/ml, and was increased to 79.6 μg/ml after grinding ($P < 0.05$). However, the addition of Pluronic F77® to the pMDI formulation decreased the solubility of TAA in the propellant blend. The solubility of the TAA and Pluronic F77® physical mixture and the co-ground TAA and Pluronic F77® formulation was 42.2 and 57.2 μg/ml, respectively. Co-grinding significantly increased the solubility of TAA in the 1:1 (w/w) P134a and P227 propellant medium compared to the physical mixture ($P < 0.05$).

4. Discussion

As seen in Table 1, the performance characteristics of the pMDI formulation were influenced by the addition of the polymeric surfactant, Pluronic F77® and by the co-grinding process. The pMDI formulations containing Pluronic F77® significantly increased the %RF of the emitted dose and co-grinding TAA with Pluronic F77® resulted in an MMAD of the emitted aerosol that is optimal for deposition in the lower respiratory tract [20]. Although, Finlay et al. reported that such changes in MMAD or RF may not give much change in lung deposition since lung deposition is only a weak function of MMAD when the GSD is large [21]. The differences in the performance characteristics are likely due to differences in the physicochemical properties of the pMDI suspension formulations. Without the polymeric surfactant, the dispersed phase of the pMDI formulation was flocculated and settled. Addition of Pluronic F77® by physical mixture with TAA decreased the time for the dispersed phase to settle and co-grinding TAA with Pluronic F77® further decreased the settling time. The factors which influence sedimentation velocity are described by Stoke's law which is written: $\nu = 2r^2 \cdot (\rho_s - \rho_0)g/9\eta_0$, where ν is the sedimentation velocity, r is the radius of the dispersed particles, ρ_s is the density of the dispersed phase, ρ_0 is the density of the dispersion medium, g is the gravitational force constant and η_0 is the intrinsic viscosity of the dispersion medium [12]. The average density of the TAA particles was found to be 1.33 ± 0.014 g/ml and was not influenced by the technique used to incorporate Pluronic F77® into the formulation. Changes in the density of the liquid propellant dispersion medium due to the addition of the soluble polymeric surfactant were assessed by measuring the vapor pressure of the pMDI formulations. Since the average vapor pressure measured for the pMDI formulations was found to be 89.1 ± 0.623 psi, the density of the propellant was not influenced by the addition of the soluble surfactant. However the vapor pressure of the pMDI formulations was found to deviate slightly from the theoretical vapor pressure of the propellant blend which was calculated by Raoult's law to be 87.1 psi.

Using the experimentally determined values for the particle size of TAA, the viscosity of the propellant, the density of TAA and the density of the propellant, the theoretical sedimentation velocities of the pMDI formulations were calculated based on the Stokes law equation. The calculated sedimentation velocities were found to be close to zero. However, visual observation of the pMDI formulations indicated that flocs were readily formed and settled rapidly. Therefore Stokes law was not useful in determining the sedimentation velocity of the drug dispersions. Stokes law is applicable only if particle-to-particle and particle-to-solvent interactions are negligible. The deviation from Raoult's law found for the pMDI formulations indicated the presence of weak intermolecular forces between the dispersed phase and the dispersion medium [12]. It is likely

that these interactions played a significant part in the characteristics of the suspension formulation since extensive flocculation of the pMDI formulations was observed. Aggregation of the dispersed phase commonly occurs in non-polar media due to the high surface area and the associated free energy of the micronized drug [22]. Suspension pMDI formulations are usually deflocculated and stabilized by the addition of surfactants [23]. Surfactants have been shown to influence the surface properties of the dispersed phase and inhibit inter-particulate interaction and flocculation by modifying the surface charge of the particles or through a steric hindrance mechanism [24]. Since co-grinding TAA with Pluronic F77® may enhance the interaction between the drug and the polymeric surfactant, changes in the characteristics of the pMDI system may be observed [7,8]. Hydrogen bonding is a common mechanism by which adsorption of the polymeric surfactant onto solid drug particles occurs [18]. This type of interaction between TAA and Pluronic F77® may be inferred by the increase in peak area of the FTIR chromatogram corresponding to the -OH stretch between 3650 and 3200 cm^{-1} and the —CH stretch in the range 3000–2840 cm^{-1} [17,18]. Furthermore, DSC thermograms presented in Fig. 3a–d show that the melting point of the TAA was increased in the presence of Pluronic F77® which may be a result of the additional energy required to break the hydrogen bonds [19]. Melting is accompanied by a positive molar enthalpy change (ΔH_{fus}) and occurs at a specific temperature. A measure of how much energy that must be added to a substance to produce a given temperature increase may be described as the molar heat capacity of the substance, $C_{P,m}$ and may be used to relate the change in enthalpy to a change in temperature [25]. The more ways (translation, rotation, vibration, intermolecular interactions) a substance has of absorbing added energy, the greater will be its $C_{P,m}$ [26]. The increased ΔH_{fus}, found in the presence of Pluronic F77® is also an indication of intermolecular interactions such as hydrogen bonding [25]. Pluronic F77® has been shown to adsorb to hydrophobic drugs and influence the physicochemical properties and surface characteristics of solid drug particles. Also, the adsorption process was shown to be influenced by the hydrophobicity and the chemical structure of the adsorbent [27]. By simple structural analysis, Pluronic F77® may be a potential proton acceptor and may hydrogen bond with the hydroxyl groups of TAA. These interactions may be enhanced by the co-grinding process and influence the extent of adsorption and the resulting steric stabilization of the suspension in the non-polar propellant medium may be increased.

Polymers act as flocculating agents in suspension formulations because part of the chain is adsorbed onto the particle surface, with the remaining parts projecting out into the dispersion medium. Formation of flocs may occur through bridging between the adsorbed portions of the polymer and by desorption of the polymer from the drug particle surface [28]. Any mechanism that may decrease the attractive energy of the suspended particles will reduce aggregation and flocculation [24]. The magnitude of the attractive energy of the suspended particles is dependent upon the relative polarity and molecular interactions between the surface of the dispersed phase and the dispersion medium. Viscosity measurements of suspension pMDI formulations has been utilized to characterize the attractive energy associated with flocculation by determining the shear force required to disrupt the flocculated system [29]. The relative viscosity of the pMDI formulations listed in Table 3 may be used to compare the inter-particulate binding strength of their dispersed phases [30]. The addition of Pluronic F77® as a physical mixture decreased the flocculation strength and co-grinding TAA with Pluronic F77® further decreased the flocculation strength of the pMDI suspension formulation. The effectiveness of a surfactant may be correlated to its extent of adsorption at the surface of the dispersed phase which in turn is influenced by its interaction with the dispersion medium. Repulsion due to steric interactions depends on the nature, thickness, and completeness of the surfactant adsorbed layers on dispersed particles [18]. Thus, enhancing the interaction between TAA and Pluronic F77® by employing the co-grinding process the surface coverage of the TAA particles by the surfactant may be increased and the particle-to-particle attraction reduced.

Differences in the aerodynamic particle size distribution of the emitted aerosols may have been due to the relative binding strength of the aggregates and their subsequent breakdown upon the application of shear forces as the aerosol was emitted from the valve of the pMDI systems. Without the polymeric surfactant, the increased MMAD of the pMDI system may be due to the spraying of particle aggregates that remain as aggregates after both the mild agitation prior to actuation and the shear forces due to passage through the valve stem [31]. The MMAD produced by the co-ground TAA and Pluronic F77® pMDI formulation was similar to the initial median particle size of the TAA prior to formulation. The formation of weakly attractive flocs in the co-ground TAA and Pluronic F77® pMDI formulation would corroborate the observed in situ sedimentation characteristics and the favorable performance characteristics of the pMDI system. An added advantage imparted by the use of the polymeric surfactant was the increase in viscosity of the liquid propellant. Physical stabilization of suspension formulations is typically enhanced by increasing the viscosity of the dispersion medium [28].

Other modifications of the physicochemical properties of the pMDI formulations, such as particle size and TAA solubility due to the addition of Pluronic F77® and the co-grinding process were also determined. The results shown in Table 4 describe the mean particle diameter of TAA after being subjected to the grinding process and after formulation and storage of the pMDI for 5 days at 25°C. The addition of Pluronic F77® either as a physical mixture or by co-grinding resulted in an increase in the median particle diameter of the TAA particles. Conversely, the median

particle size of the TAA formulated in a pMDI was found to decrease with the addition of Pluronic F77®. The differences in the particle size distributions may have been due to the influence of the polymeric surfactant on the solubility of TAA in aqueous and in the non-polar propellant dispersion medium. In Table 4 the solubility of TAA in water was found to increase in the presence of Pluronic F77®. In the presence of the surfactant, smaller particles are more readily solubilized in aqueous media than larger particles, resulting in an increase in the particle size distribution [12]. The fact that the span index decreased in the presence of the surfactant is further evidence that the smaller particles were dissolved and removed from the distribution. In the non-polar propellant medium, the opposite trend was observed. The presence of the surfactant resulted in a decrease in the median particle size of TAA after storage of the pMDI formulation for five days at 25°C. In addition, co-grinding TAA with Pluronic F77® resulted in a median particle diameter comparable to the median particle diameter of TAA before formulation. Likewise the solubility of TAA in the propellant was found to decrease by the addition of Pluronic F77®. By adsorption of the polymeric surfactant to the surface of the TAA particles, the interaction of the TAA particles with the non-polar dispersion medium was diminished and the dissolution of TAA in the propellant was reduced. The presence of the surfactant may have decreased the solubility of TAA by saturating the propellant medium and preferentially occupying the binding sites that TAA would require for dissolution to occur in the aprotic propellant solvent [32]. In addition, the adsorbed segments of the polymer may have inhibited crystal growth of a drug because they form a barrier that impedes the approach of the drug molecules from the solution to the crystal surface [12,28]. The benefit of reducing the solubility of TAA in the propellant may be further recognized in the long term since the potential of particle growth due to Ostwald ripening may be inhibited. This observation is of interest and additional studies are required to provide an explanation.

5. Conclusions

In conclusion, co-grinding TAA drug particles with Pluronic F77 promoted their interaction and possibly enhanced the adsorption of the surfactant onto the drug particle surface when formulated in a pMDI system. The interaction of TAA and Pluronic F77 influenced the dispersion, flocculation and sedimentation characteristics of a pMDI suspension formulation. Differences in the performance characteristics of the pMDI system may be attributed to interactions between TAA and Pluronic F77. In addition, the use of a polymeric surfactant may further stabilize a suspension pMDI formulation by modifying the viscosity of the propellant and decreasing drug solubility. The process of co-grinding drug particles with a polymeric surfactant may be utilized for the development of new pMDI systems containing HFA propellants that give desirable performance characteristics.

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